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Review

Role of myokines in the development of skeletal muscle insulin resistance and related metabolic defects in type 2 diabetes

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ABSTRACT

Due to its mass, skeletal muscle is the major site of glucose uptake and an important tissue in the development of type 2 diabetes (T2D). Muscles of patients with T2D are affected with insulin resistance and mitochondrial dysfunction, which result in impaired glucose and fatty acid metabolism. A well-established method of managing the muscle metabolic defects occurring in T2D is physical exercise. During exercise, muscles contract and secrete factors called myokines which can act in an autocrine/paracrine fashion to improve muscle energy metabolism. In patients with T2D, plasma levels as well as muscle levels (mRNA and protein) of some myokines are upregulated, while others are downregulated. The signalling pathways of certain myokines are also altered in skeletal muscle of patients with T2D. Taken together, these findings suggest that myokine secretion is an important factor contributing to the development of muscle metabolic defects during T2D. It is also of interest considering that lack of physical activity is closely linked to the occurrence of this disease. The causal relationships between sedentary behavior, factors secreted by skeletal muscle at rest and during contraction and the development of T2D remain to be elucidated. Many myokines shown to influence muscle energy metabolism still have not been characterized in the context of T2D in skeletal muscle specifically. The purpose of this review is to highlight what is known and what remains to be determined regarding myokine secretion in patients with T2D to uncover potential therapeutic targets for the management of this disease.

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Introduction

According to the World Health Organization, 422 million people were affected with diabetes in 2014, which amounts to 8.5% of the adult population in the world. Type 2 diabetes (T2D) is the most widespread form of this disease and its principal risk factor is excess body weight. Since skeletal muscle is a major consumer of glucose in the body due to its important mass, it plays an important role in the development of T2D [1]. Skeletal muscle of patients with T2D have been shown to develop insulin resistance (IR), as well as mitochondrial dysfunction [2,3]. A high fat diet (HFD) can cause incomplete fatty acid oxidation in the mitochondria of skeletal muscle cells [4]. The lipid metabolites (e.g. fatty acyl CoAs, acylcarnitines, ceramides and diacylglycerol) resulting from this incomplete β-oxidation interfere with insulin signalling [4–6]. For example, diacylglycerol induces the phosphorylation of Ser/Thr of IRS-1 by Protein kinase C (PKC) β/δ, while ceramides interfere with Akt phosphorylation in human skeletal muscle, both resulting in inhibition of downstream signalling and IR [7,8].

Chronic low-level inflammation is a known feature of obesity and an important factor in the development of T2D. In the white adipose tissue (WAT) of subjects with obesity, macrophages accumulate and cause chronic inflammation that eventually leads to IR. As Hotamisligil reviewed in 2017, the cytokine tumour necrosis factor-α (TNF-α) is central to the link between inflammation, obesity and T2D, but other factors are also involved.

Abbreviations: T2D, type 2 diabetes; IR, insulin resistance; hSkMCs, human skeletal muscle cells; TNF-α, tumor necrosis factor-α; IL, interleukin; WAT, white adipose tissue; EPS, electrical pulse stimulation; BMI, body mass index; HFD, high fat diet; FGF21, fibroblast growth factor 21; LIF, leukaemia inhibitory factor; SPARC, secreted protein acidic rich in cysteine; BAIBA, β-aminoisobutyric acid; ANGPTL4, angiopoietin-like 4; mtDNA, mitochondrial DNA; IMAT, intra-myocellular adipose tissue; PMAT, perimuscular adipose tissue.

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The role of these factors including other cytokines, RNAs and metabolites is not fully understood yet due to the complexity of the interaction networks between these molecules and the hierarchy in their mechanisms of action.

The efficacy of physical activity for the management of T2D has been demonstrated many times [9]. A lifestyle intervention involving regular physical activity was found to be more effective in reducing T2D incidence than Metformin treatment alone [10]. Regular exercise induced mitochondrial biogenesis and increased oxidative function in skeletal muscle, resulting in improved whole-body insulin sensitivity [11]. In contrast, physical inactivity is generally associated with higher risks of developing T2D [12]. Furthermore, sedentary behaviour such as watching television or sitting at work increased the risk of developing both obesity and T2D in individuals independently of their level of physical activity [13]. On the contrary, moderate exercise such as brisk walking for an hour daily was sufficient in reducing the risk of T2D by about 34%. In bed-rest studies, it was shown that as short as 5–7 days of inactivity in healthy volunteers resulted in increased IR [14,15]. This reduced insulin sensitivity was not related to a decreased insulin response of the liver, suggesting that sedentary behaviour induced IR primarily in skeletal muscle [15]. It was also shown that bed-rest induced a reduction in muscle mitochondrial function [16]. Taken together, the literature suggests that muscle metabolic defects affecting patients with T2D could arise from their sedentary behaviour.

Physical activity is recognized for the management of T2D, but also other diseases such as cancers, cardiovascular diseases, arthritis, depression and anxiety. How muscle contraction affects the function and physiology of distant organs is not clear, but one hypothesis is that these effects are mediated by the secretion of small peptides by contracting skeletal muscle. One of the first peptides identified to be secreted during muscle contraction was interleukin (IL)-6 [17,18]. Other factors were then shown to originate from contracting muscle and in 2003, Pedersen et al. proposed that cytokines originating from skeletal muscle should be called myokines [19]. This group also described the role of IL-6 in regulating muscle energy metabolism and reducing chronic low-grade inflammation. Both chronic and acute exercises regulate myokine secretion (Fig. 1). Other factors than myokines are secreted during muscle contraction such as RNAs and metabolites to form the muscle secretome [20]. Myokines can improve muscle metabolism locally or be released in the circulation to act in an endocrine fashion to improve the function of other organs such as the liver, pancreatic β cells or adipose tissue [21,22]. Interestingly, myokines are secreted differently in patients with T2D. Indeed, the myokine profile of human primary skeletal muscle cells (hSkMCs) from patients with T2D is different from insulin sensitive hSkMCs [23]. Since the muscle secretome has only recently drawn attention in the context of metabolic diseases, few studies have been completed for the comparison of myokine secretion between individuals with IR/T2D and healthy subjects. Circulating levels of some myokines are down regulated in patients with T2D in comparison to healthy subjects, while others are increased [24]. This suggests that myokine secretion and/or signalling is altered in people with T2D and it is possible that the lack of physical activity in people with T2D [12] results in these alterations. Since myokines are known to increase muscle insulin sensitivity and mitochondrial function, an alteration in myokine secretion in patients with T2D could potentially lead to skeletal muscle IR and mitochondrial dysfunction (Fig. 2). Therefore, the purpose of this review was to clarify the role of

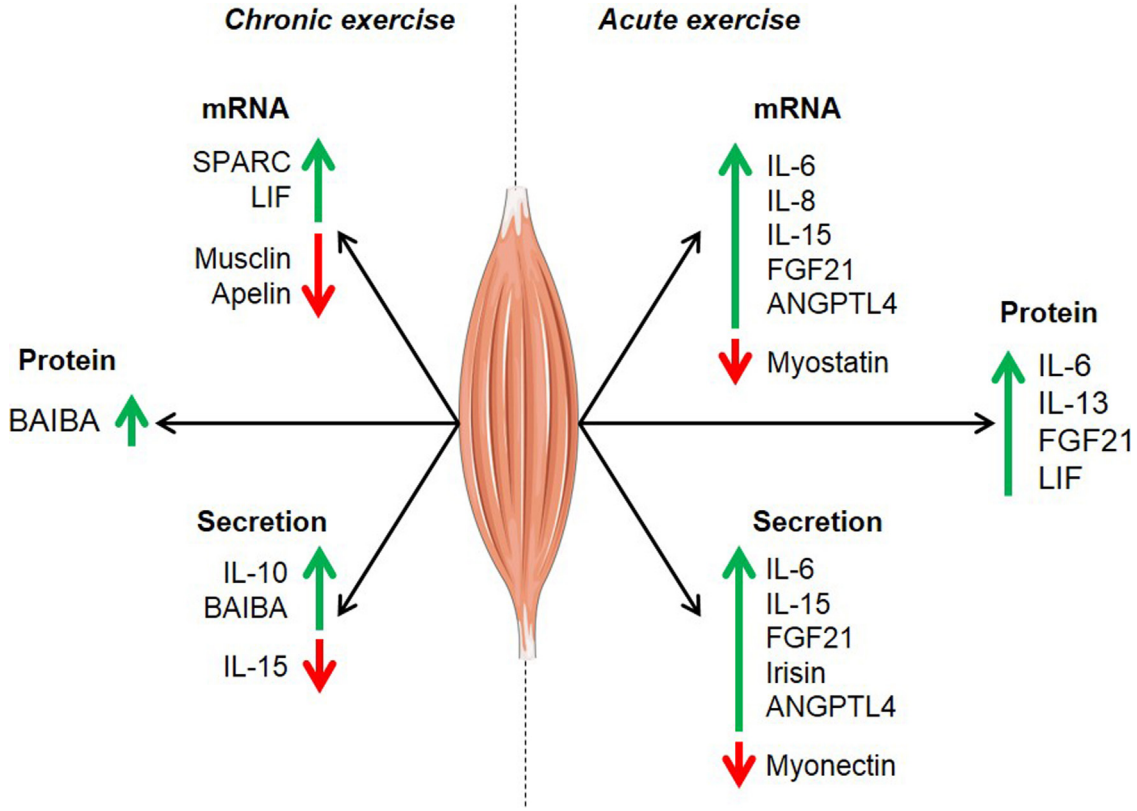

Fig. 1. Regulation of myokine secretion by acute and chronic exercise. Acute and chronic physical activity result in different alterations of myokine expression at the mRNA or protein levels in skeletal muscle and of myokine secretion in circulation. Expression and/or secretion of most recognized myokines is increased by acute and/or chronic exercise, but some myokines are decreased in response to exercise.

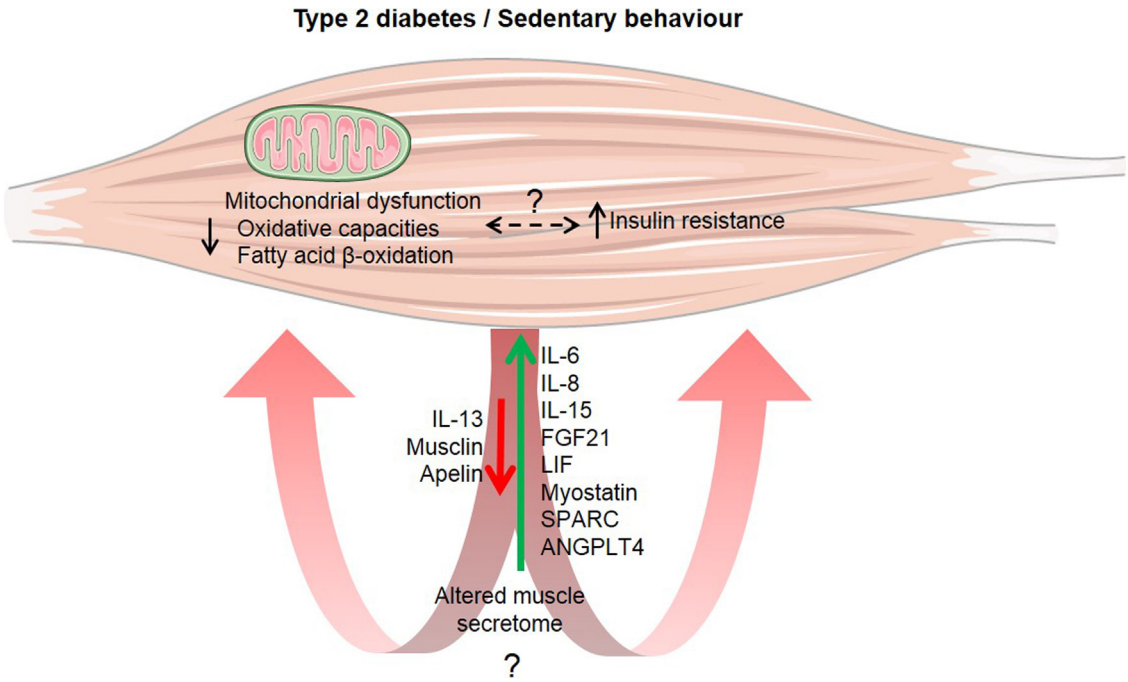

Fig. 2. Hypothetical mechanism of the development of muscle metabolic defects during type 2 diabetes and the potential involvement of myokines in this process. The muscle secretome (i.e. secretion of myokines, RNAs, mtDNA and metabolites) is altered in the context of type 2 diabetes and/or sedentary behavior. This altered muscle secretome can potentially lead to an altered mitochondrial function and/or insulin resistance development in skeletal muscle.

myokines potentially involved in the development of muscle IR and mitochondrial dysfunction. The focus of the review is on the autocrine/paracrine effect of myokines in altering energy metabolism of skeletal muscle cells in the context of T2D. A major challenge in the observation of autocrine/paracrine effects of myokines on muscle energy metabolism is the fact that circulating levels of these peptides are not reflective of their interstitial concentrations within skeletal muscle. During muscle contraction, certain myokines are released into the circulation, but others remain in the muscle interstitium to act locally. To better understand the effect of contraction-induced myokines on skeletal muscle metabolism, it is crucial to focus on the local levels of these peptides.

Interleukin 6

Back in 2005, Petersen and Pedersen reviewed the role of IL-6 in the development of metabolic disease and proposed that this myokine could serve as a marker of T2D rather than a cause as it was previously believed [25]. IL-6 was the first identified myokine and is a particular cytokine since it can be produced by almost any cell type with the right stimulus [26] (i.e. TNF-α treatment induces IL-6 expression in fibroblasts) [27]. This particularity could explain why studies in the literature focusing on levels of IL-6 in IR conditions are contradictory and differ according to the tissue. As Pedersen and Febbraio described it, "the role of IL-6 in inflammation is context dependent" [28]. Systemic levels of IL-6 are elevated in the context of obesity and T2D and it has been shown that plasma IL-6 levels are correlated to whole-body adiposity [29]. This suggests that high systemic levels of IL-6 are related to poor metabolic outcomes (i.e. development of IR, obesity, impaired fatty acid oxidation). That said, several studies have shown the inhibitory effect of IL-6 on TNF-α [25]. TNF-α is a main factor of chronic low-grade inflammation that has been identified as one cause for the development of IR [30]. IL-6 could then be involved in reducing chronic inflammation by inhibiting TNF-α production.

In skeletal muscle, IL-6 is acutely induced by contraction: circulating IL-6 levels can be increased up to 100-fold in response to an acute bout of exercise [18]. It has also been demonstrated that IL-6 ameliorates insulin-stimulated glucose disposal probably through its positive effect on muscle energy metabolism (increase in muscle glucose uptake, insulin sensitivity and fatty acid oxidation) [31]. The improved glucose conversion to glycogen, as well as the increase in fatty acid β-oxidation with acute and chronic treatment of muscle cells with supra-physiological concentrations of IL-6 is mediated by the AMPK pathway [31,32]. It was also shown that acute supra-physiological treatment with recombinant human IL-6 increased lipid oxidation in muscle without affecting WAT lipolysis, suggesting an autocrine/paracrine role of muscle-secreted IL-6 in increasing lipid metabolism [33]. That said, this finding does not exclude the possibility that chronic IL-6 exposure could eventually lead to increased fatty acid release from WAT to provide substrates for muscle β-oxidation, as the researchers highlighted. High levels of IL-6 in skeletal muscle seem to have a different effect depending on the exposure time. As demonstrated by Nieto-Vazquez et al., acute IL-6 treatment of hSkMCs increased insulin stimulated glucose uptake, while chronic treatment led to impaired insulin signalling [34]. This feature of IL-6 signalling resembles ROS production within skeletal muscle, which is very acute during a bout of exercise and modulates energy metabolism positively, while in the context of T2D, its chronic elevation leads to the development of skeletal muscle IR [35]. An acute increase in IL-6 secretion during exercise could then be beneficial for muscle energy metabolism, while a chronic elevation of IL-6 secretion in the context of T2D could lead to IR and mitochondrial dysfunction.

Muscle *IL-6* mRNA levels as well as circulating IL-6 has been measured in healthy individuals and patients with T2D in response to an acute bout of exercise [36]. No differences were found in the expression of *IL-6* mRNA after exercise between healthy and T2D muscle, but results suggest a trend towards a greater increase in muscle *IL-6* mRNA expression after exercise in patients with T2D.

Also, their results showed no correlation between plasma IL-6 and mRNA in muscle, suggesting that other tissues contribute to circulating levels of IL-6. Increased circulating levels of IL-6 in the context of T2D and obesity could be explained by adipose tissue inflammation rather than the muscle secretion of this cytokine. As far as we know, IL-6 concentration in muscle interstitium specifically has not been compared between healthy subjects and patients with T2D. However, cultured hSkMCs from patients with T2D secrete more IL-6 at rest than hSkMCs from non-diabetic subjects [23], suggesting that increased circulating IL-6 in patients with T2D could be accountable to muscle secretion. Unfortunately, to our knowledge, IL-6 secretion after muscle contraction in the interstitial space or electrical pulse stimulations (EPS), which mimics muscle contraction in vitro, of hSkMCs has not been compared between insulin sensitive and IR individuals. On the other hand, Jiang et al. demonstrated that human hSkMCs obtained from participants with T2D respond differently to IL-6 treatment than healthy hSkMCs [37]. Indeed, IL-6 treatment did not increase glucose uptake in IR hSkMCs as much as in healthy hSkMCs, but the positive effect on lipid oxidation was similar in both conditions. This suggests that IL-6 signalling is partially altered in hSkMCs from patients with T2D. Their increased IL-6 secretion might be a compensation mechanism to counteract the alteration in muscle IL-6 signalling, similar to increased insulin secretion in the context of IR. Taken together, these studies suggest that muscle from patients with T2D are "IL-6 resistant". Further investigations would be required to test that hypothesis.

Interleukin 8

It has been reported in healthy subjects that *IL-8* mRNA is increased up to 10-fold in muscle after exercise and up to 2-fold in a model of myotube contraction [38]. Nielsen and Pedersen suggested that since *IL-8* mRNA is dramatically increased by exhaustive exercise (3 h of treadmill running) as an inflammatory response and increased to a lesser extent in muscle after a bout of exercise of moderate intensity (1 h of cycling), but circulating IL-8 is not significantly increased in these conditions, this myokine might act on muscle in an autocrine/paracrine manner [39]. In this sense, it was shown that EPS stimulation of hSkMCs induced an increase in IL-8 secretion, further confirming the secretion of IL-8 by muscle cells [40].

This cytokine has previously been associated with obesity and/or IR through positive correlations between circulating levels of IL-8 and BMI (body mass index), as well as HOMA-IR [41]. In hSkMCs affected with IR, IL-8 secretion was found to be increased significantly [42]. Similarly, IL-8 secretion was increased in hSkMCs and skeletal muscle tissue explants from patients with T2D in comparison to healthy subjects [23,43]. That said, circulating IL-8 levels were not different between the two subject groups, which contradicts the results of Zozulinska et al. who had found elevated levels of plasma IL-8 in patients with T2D compared to healthy subjects [44]. The role of IL-8 in the development of skeletal muscle IR remains unclear since most studies on this myokine in the context of T2D focused on circulating levels of this inflammatory factor, which do not seem to represent the level of the myokine in muscle interstitium.

Interleukin 10

IL-10 is a cytokine expressed in numerous tissues such as the heart, liver and adipose tissue, as well as skeletal muscle. In a model of IR in mice, Hong et al. demonstrated the protective effect of supra-physiological levels of IL-10, as well as muscle specific overexpression of IL-10 in the reduction of IR and inflammation in skeletal muscle [45]. Similarly, obese mice overexpressing muscle specific IL-10 were gaining weight under a HFD, but their muscle insulin signalling capacities and glucose metabolism were increased [46]. Since IL-10 acts in a positive way on skeletal muscle metabolism, it is of interest for the study of its role in the development of IR and mitochondrial dysfunction. Interestingly, it has been shown that low production capacity of circulating IL-10 in response to inflammation is associated with T2D, meaning that patients with T2D secrete IL-10 differently in response to an inflammatory stimulus [47]. In a recent study, patients with T2D underwent a 12-week high intensity interval training exercise program and plasma quantification of IL-10 revealed no change in levels of this myokine after an acute bout of exercise, but a significant increase at the end of the intervention in the resting state [48]. Unfortunately, to date, IL-10 secretion by skeletal muscle cells per se has not been detected in response to contraction in vivo or in vitro [23,40]. Since this myokine seems to induce positive muscle metabolic changes in an autocrine/paracrine manner, measuring the levels of IL-10 in muscle interstitial space in the context of T2D would be more informative than only quantifying its circulating levels.

Interleukin 13

IL-13 is a contraction-induced myokine that has been studied for its positive effect on energy metabolism [40]. Indeed, Darkhal et al. showed that the global overexpression of IL-13 in mice reduced the inflammatory response and the development of IR caused by a HFD [49]. Interestingly, IL-13 levels in serum and secretion from hSkMCs were shown to be lower in patients with T2D, but not the muscle mRNA expression or the presence of IL-13 receptor (IL-13RA1) [50]. The authors suggested that this implied a post transcriptional regulation mechanism of IL-13 in which unknown T2D related factors were involved. Myotubes from individuals with T2D did not show an equivalent increase in basal glucose uptake after exposition to IL-13 as obtained in healthy hSkMCs, although glucose oxidation was similar, suggesting a partially altered IL-13 signalling pathway in the context of T2D. Further exploration of the mechanisms regulating IL-13 secretion in the context of T2D could help better understand how this myokine modifies muscle energy metabolism and how the response to IL-13 signalling can be improved in IR muscle.

Interleukin 15

IL-15 was first described as expressed in skeletal muscle in 1995 by Quinn et al., where it was found to induce muscle fibre hypertrophy. A significant correlation between body composition markers (i.e. BMI, trunk fat and total body fat percentage) and circulating IL-15 levels has been shown in humans. Body composition correlated negatively with IL-15 in plasma, while T2D status did not [51]. However, a more recent study showed an increase in plasma IL-15 in patients with T2D and a down regulating effect of chronic exercise on basal circulating levels of IL-15 regardless of body composition [52]. An increase in resting IL-15 secretion by hSkMCs from T2D patients in comparison to healthy subjects was also found [23].

In mice, it was shown that IL-15 was necessary for the positive effect of exercise on muscle PPARδ pathway activation [53], suggesting IL-15 is at least in part involved in the positive effect of exercise on muscle oxidative capacities. In a mouse model, muscle *IL-15* mRNA content was found to be reduced by HFD-induced obesity, while treadmill running increased muscle *IL-15* mRNA [54]. This contraction induced increase in muscle *IL-15* mRNA was also observed in humans after resistance exercise

[55]. Contradictorily, no alteration in muscle *IL-15* mRNA was found after exercise in obese subjects with or without T2D, while plasma IL-15 levels increased [36]. These discrepancies in the literature regarding muscle and circulating levels of IL-15 in the context of T2D and/or in response to exercise might be due to the intricate role of the subunit α of the IL-15 receptor (IL-15Rα). The secreted form of IL-15Rα (sIL-15Rα) can be an agonist or an antagonist of IL-15 depending on the cell type. The methods used to measure circulating IL-15 in the above mentioned studies were not necessarily ascertained as specific to the free form of IL-15, which might be the active form of the myokine that targets muscle cells. The complexed form (IL-15/sIL-15Rα) might also have been detected in these studies (reviewed in [56]). Further observations focusing on the quantification of the free form of IL-15 and IL-15/sIL-15Rα in muscle interstitium, especially after muscle contraction, could help unveil the potential role of this myokine in T2D.

Interleukin 18

IL-18 is a cytokine expressed in various human tissues including skeletal muscle and is found mostly in type II glycolytic fibres [57]. Around fifteen years ago, Aso et al. demonstrated that systemic levels of IL-18 were significantly increased in the context of T2D [58]. More recently, IL-18 treatment was found to increase muscle lipid oxidation in IR mice through the AMPK pathway [59]. These findings suggest that high levels of IL-18 in the plasma might be related to a chronic inflammation status, while an acute increase of this myokine in muscle improves its metabolic functions. Nonetheless, to our knowledge, no studies have shown the effect of muscle contraction on the secretion and/or muscle mRNA expression of IL-18.

Musclin

Musclin is a myokine known for its potential involvement in the development of IR [60]. A recent study showed that plasma levels of musclin were positively correlated to some indicators of T2D such as fasting plasma glucose and triglycerides, as well as whole-body IR [61]. This finding is supported by an earlier study from Liu et al., who showed that exposition of rat muscle cells to musclin reduced glucose uptake by inhibiting insulin signalling through Akt [62]. Another study showed an increase in muscle protein and mRNA levels of musclin in IR rats in comparison to controls [63]. The same group showed a reduction of the expression of musclin mRNA in muscle of IR rats after an exercise intervention [64]. Since this myokine seems to be, at least in part, involved in the development of IR, further studies on musclin levels in muscle after an acute bout of exercise, as well as a comparison in the exercise response between muscle cells from healthy subjects and patients with T2D are needed. The secretion of musclin in response to muscle contraction has yet to be demonstrated.

Fibroblast growth factor 21

Fibroblast growth factor 21 (FGF21) secretion from muscle of patients with T2D is increased [65]. It has been suggested that this myokine is involved in IR, which was supported by Lindegaard and colleagues who demonstrated that *FGF21* mRNA expression is increased in skeletal muscle of individuals with IR but not in their plasma [66]. Recently, it was shown that first-degree family history of T2D is not a predictor of elevated circulating FGF21 levels [67]. This suggests that the elevation of FGF21 in the plasma does not precede T2D, but it does not rule out elevated muscle *FGF21* mRNA as an early event in the development of this disease. Interestingly, Voigt et al. found that induction of FGF21 expression by mitochondrial stress reduced IR in a diabesity mouse model [68]. The positive effects of this myokine on metabolic disease were mediated by its stimulation of adiponectin secretion [69]. Adiponectin is produced by adipose tissue and is down regulated during obesity and T2D, causing a reduction in muscle fatty acid oxidation and insulin sensitivity [70]. Conversely, FGF21 was increased in the circulation, as well as at the mRNA and protein levels in muscle after an acute bout of exercise [71]. Others found that eccentric exercise had no effect on either muscle FGF21 content or release in the circulation, although they did detect an increase in fibroblast activator protein alpha (FAP), which negatively regulates FGF21 activity [72]. They did not detect FAP release from skeletal muscle, which indicates this mechanism of regulation might not be related to muscle contraction per se, but rather to other metabolic adaptations to exercise. Also, the authors mentioned that the eccentric exercise applied was submaximal, which is sufficient to induce IL-6 secretion by muscle, but could be insufficient for the release of FGF21 in the circulation since the stress component of more strenuous exercise is absent. In a recent study by Sabaratnam et al., an acute exercise bout induced a rise in muscle *FGF21* mRNA and FGF21 released in the circulation that was further increased 3 h in the recovery period in both healthy subjects and patients with T2D [36]. Although the authors did not address it, there seemed to be a trend towards overall decreased expression of muscle FGF21 in the diabetic group. Unfortunately, the study design did not take into account the quantification of the active form of FGF21, but rather its total form. That said, it was demonstrated previously that exercise did not alter the active/total form ratio of FGF21 released into the circulation [72]. The study of FGF21 secretion from isolated hSkMCs in the context of T2D would help validate some of the findings in muscle expression and release into the circulation of this myokine.

Irisin (FNDC5)

In 2012, Boström et al. first characterized irisin as an exercise-induced hormone that mediates the browning of WAT [73]. As Perakakis et al. thoroughly reviewed at the beginning of 2017, irisin plays a role in glucose homeostasis, notably by ameliorating IR [74]. The precursor mRNA for irisin, FNDC5, is mostly expressed in muscle tissues. In fact, it was shown in humans that FNDC5 is present up to more than 200-fold in skeletal muscle cells in comparison to adipocytes [75]. This group also found that muscle mRNA expression and circulating irisin levels associated negatively with the status of IR and obesity. Others also found that irisin levels are inversely correlated with the prevalence of T2D and that elevated serum irisin is associated with a reduced risk of developing T2D [76]. In hSkMCs from patients with T2D, study of the suppressive effect of glucose on the expression of FNDC5 has suggested that hyperglycaemia negatively regulates *FNDC5* mRNA expression [77]. Strikingly, secreted levels of irisin from hSkMCs of patients with T2D were found to be higher than in healthy hSkMCs. That said, it was also shown that serum irisin correlates positively with IR, even after adjusting for BMI to exclude obesity related factors [78,79]. Results for either circulating or skeletal muscle irisin levels measured in humans differ greatly between studies and many contradictions can be found in the literature regarding their implication in metabolic disease, as Sanchis–Gomar et al. highlighted in 2014. To this end, Albrecht et al. tested several commercial irisin ELISA kits and found them highly unspecific, which could account for the discrepancies in studies of this myokine [80]. To solve this problem, Jedrychowski et al. used mass spectrometry to measure irisin levels in the plasma of subjects before and after aerobic exercise [81]. They found a significant increase in irisin levels after exercise, thereby suggesting its

involvement in the beneficial effects of physical exercise in muscle energy metabolism. Irisin treatment in vitro was shown to increase oxidative capacity in muscle while inducing the expression of several metabolic genes involved in mitochondrial biogenesis without activating an inflammatory response [82,83]. Also, in a HFD-induced rat model of IR, irisin administration improved insulin sensitivity and promoted weight loss, while exercise induced an increase in circulating levels of irisin and similar metabolic improvements [84]. Since irisin is a contraction-induced myokine with overall beneficial effects on energy metabolism, a comparison in the secretion of this protein in response to muscle contraction in patients with T2D and healthy subjects would help better understand how it influences muscle metabolic defects.

Apelin

Apelin is a cytokine that has recently been identified as a myokine in a human exercise study showing that muscle from obese individuals submitted to a chronic exercise training regimen had increased apelin mRNA [85]. HSkMCs from these subjects cultured in vitro secreted apelin significantly, confirming apelin as a new contraction-induced myokine. Since the increase in muscle apelin mRNA correlated with insulin sensitivity improvements from exercise, but that its levels were not increased in plasma, the authors proposed that apelin may act in an autocrine/paracrine fashion on muscle. Recently, apelin expression in muscle was found to be up regulated by chronic exercise in mice, and apelin secretion was increased after in vitro EPS of hSkMCs [86]. Vinel et al. also demonstrated that apelin promoted muscle hypertrophy through AMPK activation, as well as mitochondrial biogenesis (increased mitochondrial DNA (mtDNA)) and enhanced mitochondrial function (enhanced citrate synthase and aconitase activities and improvements in mitochondrial morphology through increased cristae formation). These findings support the notion that apelin may act in an autocrine/paracrine fashion to induce muscle adaptations to exercise. Apelin treatment in HFD mice improved insulin sensitivity by increasing mitochondrial biogenesis through the AMPK pathway, thereby ameliorating complete fatty acid oxidation and reducing the production of acylcarnitines in skeletal muscle [87]. Muscle apelin levels in rodent models of T2D were shown to be decreased in comparison to healthy controls [88]. However, results demonstrated that basal plasma apelin levels were higher in patients with obesity and T2D compared to healthy controls. Dray et al. also showed a positive relation between apelin levels in plasma and insulin, glucose and HbA1c levels in humans, supporting the idea that this myokine is increased in the context of T2D [88]. Fasshauer and Bluher proposed that this increase in circulating apelin in the context of obesity and T2D might be a sign of apelin resistance [89]. Apelin is also expressed and secreted by adipocytes, and circulating apelin levels were found to be elevated in the context of obesity [90]. Since apelin secretion is regulated by the presence of insulin, impaired insulin sensitivity leading to hyperinsulinemia could lead to increased plasma apelin in patients with T2D. Further explorations of apelin secretion in skeletal muscle in the context of T2D are needed to better assess the role of this myokine in the development of muscle IR.

Myonectin – C1q tumour necrosis factor α-related protein isoform 5 (C1QTNF5)

Serum levels of myonectin were shown to be elevated in rodent models of diabetes [91]. Increased circulating myonectin correlated with lower mtDNA content in L6 rat myocytes, drawing a link with mitochondrial dysfunction, while myonectin treatment resulted in improved glucose uptake through activation of the AMPK pathway. Higher myonectin mRNA expression might be a compensatory mechanism for the depleted mitochondrial content in skeletal muscle affected with IR. It was shown that aerobic exercise decreased myonectin levels in plasma, which correlated with the increase in insulin sensitivity and the improvement in mtDNA content in leukocytes from blood samples [92]. Unfortunately, muscle mtDNA and insulin sensitivity were not measured in these participants. Further research would be necessary to assess the definite role of myonectin in promoting IR and/or mitochondrial dysfunction in muscle in the context of T2D.

Leukaemia inhibitory factor

Leukaemia inhibitory factor (LIF) has been shown to promote myoblast proliferation. Broholm et al. demonstrated an increase in LIF secretion by cultured hSkMCs after EPS [93]. It was also shown that LIF is increased in human muscle after exercise, but not in circulation, suggesting this myokine is most likely a regulator of myoblast proliferation by acting in an autocrine fashion. The same group investigated whether muscle LIF and LIF receptor (LIFR) mRNA and protein content would be different in patients with T2D in comparison to healthy subjects. They found that both LIF and LIFR levels were increased in muscle and myoblasts from patients with T2D in comparison to healthy controls [94]. LIF treatment in hSkMCs from patients with T2D did not result in increased proliferation or STAT3 signalling as in cells from healthy subjects, suggesting that the signalling pathways of this myokine are altered in this context. However, another study in mice showed that LIF increased glucose uptake in muscle independently of IR status [95]. In a study focusing on cardio metabolic disease, interval training induced an increase in LIF muscle expression, thereby reversing muscle atrophy linked to myocardial infarction [96]. Since LIF is induced by muscle contraction, it would be interesting to see how this myokine is secreted in patients with T2D during exercise for the improvement of muscle metabolic functions.

Myostatin

Myostatin is a myokine known to influence skeletal muscle growth and to be involved in glucose homeostasis, as it stimulates glucose uptake and oxidation through the AMPK pathway [97]. However, in mice fed a HFD, suppression of myostatin by peptibody leads to increased insulin sensitivity through an increase in Akt signalling, as well as glucose transporter GLUT4 expression in muscle [98]. The peptibody treatment also inhibited macrophage infiltration in adipose tissue and expression of pro-inflammatory cytokines in muscle. This study also showed a negative regulation of irisin by myostatin, which could explain the positive metabolic effects of myostatin inhibition in skeletal muscle. Myostatin inactivation increased fatty acid oxidation by improving mitochondrial function in muscle of mice on HFD [99]. However, myostatin deletion was also shown to lead to impaired mitochondrial function and decreased mitochondrial content in a mouse knockout of this myokine [100]. Plasma myostatin levels were found to be significantly lower in patients with T2D in comparison to insulin sensitive subjects [79]. Interestingly, a negative correlation between myostatin and irisin levels was detected in the circulation of patients with T2D, but not in their insulin sensitive counterparts. Contradictorily, in three different groups of obese subjects: patients with T2D, prediabetes and insulin sensitive individuals, an increase in plasma myostatin was shown relative to diabetic status [101]. This last finding suggests that there might be a mechanism of compensation in the

skeletal muscle of patients with T2D to improve the impaired glucose metabolism by increasing the production of myostatin. Myostatin also positively correlated with factors predictive of T2D such as fasting plasma glucose and IR, advocating that it might be involved in the pathogenesis of T2D. The authors highlighted that some of the studies presenting a negative relation between T2D and circulating myostatin involved long standing patients with T2D that had been administered antidiabetic drugs for some time, which might influence muscle myostatin secretion. In another study, while only slight differences were found for myostatin levels in the plasma of patients with T2D compared to insulin sensitive subjects, in skeletal muscle, myostatin mRNA levels were significantly higher in patients with T2D [102]. In severely obese patients, myostatin secretion from isolated myoblasts, expression in skeletal muscle and circulating levels were all up regulated in comparison to healthy subjects and correlated positively with IR [103]. What is particularly interesting with myostatin is that its muscle mRNA expression is down regulated by resistance and aerobic exercises [104]. Further investigations are needed to establish more clearly how myostatin function and/or signalling is altered in the context of T2D in skeletal muscle.

Secreted protein acidic and rich in cysteine

Secreted protein acidic and rich in cysteine (SPARC) is a contraction-induced myokine that has been shown to activate the AMPK pathway in rat muscle cells, influencing glucose metabolism independently of insulin action [105]. In hSkMCs obtained from healthy subjects that followed a strength training intervention, *SPARC* mRNA was found to be increased with regular exercise [106]. However, in db/db mice, plasma and skeletal muscle levels of SPARC were significantly increased, as well as muscle *SPARC* mRNA content [107]. Similarly, in humans, plasma levels of SPARC were found to be positively correlated to BMI, fasting plasma insulin, triglycerides and HOMA-IR, suggesting a role for this myokine in the pathogenesis of T2D [108]. Since SPARC is believed to have a positive effect on muscle energy metabolism, it seems that its signalling in muscle of patients with T2D is impaired.

β-aminoisobutyric acid

β-aminoisobutyric acid (BAIBA) is another exercise-induced myokine that acts on skeletal muscle to prevent T2D related metabolic defects. It was demonstrated that BAIBA treatment reduced IR and increased fatty acid oxidation in both C2C12 mouse myocytes and skeletal muscle of mice on HFD [109]. Also, in a mouse model of T2D, BAIBA treatment improved IR and reduced fasting blood glucose [110]. In wild-type mice, chronic exercise significantly increased BAIBA secretion from skeletal muscle and plasma levels of this myokine [111]. To our knowledge, no study has investigated the secretion and/or expression levels of BAIBA in skeletal muscle of patients with T2D in comparison to healthy subjects.

Angiopoietin-like 4

Angiopoietin-like 4 (ANGPLT4) expression is increased in mouse skeletal muscle after an acute exercise bout in relation with the activation of the AMPK pathway [112]. This study also showed that physiological concentrations of ANGPLT4 treatment in C2C12 cells increased mitochondrial function. Nevertheless, it was demonstrated that genetic inactivation of ANGPLT4 ability to inhibit lipoprotein lipase in human improved glucose homeostasis and decreased overall risk of developing T2D [113]. It was also found that plasma ANGPLT4 levels were increased in subjects with impaired glucose tolerance and correlated positively with T2D markers such as HbA1c and HOMA-IR [114]. In addition, muscle *ANGPLT4* mRNA was increased in a mouse model of T2D [115]. In hSkMCs, *ANGPLT4* mRNA was found to be significantly expressed at rest and increased by treatment with long-chain fatty acids in a PPAR-δ-dependant manner [116]. This group found that plasma ANGPLT4 was likely not involved in muscle lipid breakdown although it did correlate with muscle *ANGPLT4* mRNA expression. Nonetheless, ANGPLT4 produced locally in skeletal muscle regulated WAT lipolysis. Recently, it was found that muscle ANGPLT4 mRNA and plasma levels of this myokine were increased after acute exercise and further increased 3 h into recovery in humans, while in the context of T2D, levels of muscle *ANGPLT4* mRNA seemed to be higher in all conditions [36]. This myokine involved in the energy metabolism adaptations of exercise seems to have altered signalling in patients with T2D, but the implications of this manifestation are not known as of yet.

Exploiting myokines for the treatment of type 2 diabetes

As discussed in the present review, in the context of T2D, the expression and production of myokines from skeletal muscle is altered (Table 1). Some myokines are up regulated, while others are down regulated. Also, the changes in myokines released in the circulation do not always reflect the expression of these peptides in skeletal muscle and vice-versa. A number of myokines improve muscle energy metabolism (i.e. insulin sensitivity, glucose uptake, mitochondrial function, fatty acid oxidation, etc.). Since T2D translates to impaired muscle energy metabolism, this raises the question: is altered myokine secretion involved in the development of metabolic defects during T2D? Why are myokine expression and secretion altered in the context of T2D? Multiple hypotheses could explain this alteration: physical inactivity in patients with T2D could modify their myokine profile, a hyperglycaemic environment could regulate their expression and secretion within muscle or systemic inflammation could interfere with myokine signalling due to the secretion of cytokines by adipocytes and macrophages. Another hypothesis that has been brought forward by many research groups is the concept of myokine resistance, or an impaired response to myokine signalling in skeletal muscle that could lead to an alteration of their expression and secretion within muscle tissue. This particular hypothesis could help explain why certain myokines with a positive effect on energy metabolism (i.e. IL-6, IL-13, irisin, FGF21, SPARC, ANGPTL4, etc.) are up regulated in the context of T2D. The signalling pathways of these myokines might be impaired in patients with T2D or their upregulation might be a compensatory mechanism for the metabolic defects occurring in skeletal muscle.

Ever since the discovery of myokines and the regulation of their secretion by muscle contraction, numerous research groups have proposed the possibility of using these factors for the treatment of metabolic diseases. In a review published at the beginning of 2018, J.Y. Huh proposes that myokines released by muscle could be a mechanism of adaptation of this organ to the increase in glucose demand during contraction. This theory could explain in part why myokine secretion is altered in patients with T2D since fasting blood glucose and insulin levels are elevated in these conditions. Another interesting idea brought forward by this author is the synergy in regulation of myokines secreted by muscle cells. Many myokines have been proven to be regulated in part by other myokines, for example myostatin and irisin whose levels are usually inversely correlated, especially in the context of T2D. This cooperative action of myokines during muscle contraction and exercise could explain the complexity of the effect it has on energy metabolism, specifically in the context of T2D. The altered

Table 1
Secretion of myokines is altered by muscle contraction, regular exercise and T2D.

Myokine	Influence on muscle energy metabolism	Regulation by muscle contraction	Regulation by chronic exercise	Muscle levels in IR	Plasma levels in IR
IL-6	↑ glucose metabolism (27) ↑ fatty acid oxidation (27,28) ↓ glucose metabolism chronic exposure (29)	↑ muscle protein (15) ↑ mRNA and plasma protein (31)		↑ protein from hSkMCs (20)	↑ (25)
IL-8		↑ mRNA (32)		↑ protein from hSkMCs and muscle (20,38)	↑ (36,39) = (38)
IL-10	↑ insulin sensitivity (40) ↑ glucose metabolism (41)	= plasma protein (43)	↑ plasma protein (43)		↓ secretory response (42)
IL-13	↑ insulin sensitivity (44) ↑ glucose uptake (45)	↑ protein (35)		↓ protein from hSkMCs = mRNA (45)	↓ (45)
IL-15	↑ oxidative capacities (48)	↑ mRNA (49,50)	↓ plasma protein (47)	↑ protein from hSkMCs (20)	↓ (47)
IL-18	↑ lipid oxidation (54)				↑ (53)
Musclin	↓ glucose uptake and insulin sensitivity (57)		↓ muscle mRNA (59)	↓ protein and mRNA (58)	↑ (56)
FGF21	↑ insulin sensitivity (63,64) ↑ fatty acid oxidation (64)	↑ plasma protein, muscle mRNA and protein (31,66)		↑ protein (60) ↑ mRNA (61)	= (61)
Irisin	↑ oxidative capacities and mitochondrial biogenesis (77,78) ↑ insulin sensitivity (79)	↑ plasma protein (76,79)		↓ mRNA (70) ↑ protein from hSkMCs (72)	↓ (70,71) ↑ (73,74)
Apelin	↑ insulin sensitivity, fatty acid oxidation and mitochondrial biogenesis (81)		↓ muscle mRNA (80)	↓ protein (82)	↑ (82)
Myonectin	↑ glucose uptake (85)	↓ plasma protein (86)			↑ (85)
LIF	↑ glucose uptake (89)	↑ protein from hSkMCs and muscle (87) = plasma (87)	↑ muscle mRNA (90)	↑ protein from hSkMCs and muscle (88)	
Myostatin	↑ glucose uptake and oxidation (91)	↓ muscle mRNA (98)		↑ muscle mRNA (96,97) ↑ protein from hSkMCs (97)	↑ (95,97)
SPARC	↑ glucose uptake (99)		↑ hSkMCs mRNA (100)	↑ muscle mRNA and protein (101)	↑ (101,102)
BAIBA	↑ insulin sensitivity and fatty acid oxidation (103,104)		↑ muscle and plasma protein (105)		
ANGPTL4	↑ mitochondrial function (106)	↑ muscle mRNA (31,106) ↑ plasma protein (31)		↑ muscle mRNA (109)	↑ (108)

↑: upregulated; ↓: downregulated; =: unchanged; numbers in (...) refer to references in the text.

secretion of one myokine could create a butterfly effect on other myokines resulting in the alteration of skeletal muscle glucose and lipid metabolisms.

As mentioned before, the relationship between sedentary behaviour and the prevalence of T2D has been explored by many groups and a clear correlation has been drawn between lack of physical exercise and the development of IR, especially in the context of obesity [13]. Also, the levels of many myokines have been studied in individuals before and after following a training program to observe variations in their secretion in response to regular exercise. Some myokines are found to be up regulated in trained individuals in comparison to sedentary subjects, while other myokines are down regulated in the context of regular physical activity. For example, chronic exercise upregulates IL-6, IL-10, FGF21, irisin, LIF, BAIBA and apelin, while it downregulates myostatin, myonectin and musclin [36,48,64,84,85,92,96,111] (Fig. 1). This suggests that the alteration in myokine secretion in patients with T2D could be explained by the lack of physical exercise in their lifestyle. To verify this hypothesis, the skeletal muscle myokinome, as proposed by Nikolić et al. in 2017, of patients with T2D should be investigated to find a potential correlation between the T2D profile and their level of physical activity.

Another factor that could explain the differences in myokine secretion between healthy subjects and patients with T2D is the state of chronic low-grade inflammation. Since many myokines are also cytokines, some of them are also secreted by other tissues and act as inflammatory factors when released in the circulation by immune cells. Therefore, it is difficult to determine if the alteration in myokine secretion in plasma/serum is due to systemic inflammation or altered skeletal muscle secretion. As reviewed in 2017 by Kalinkovich and Livshits regarding obesity and sarcopenia, some myokines are exacerbated by adipose tissue inflammation, which results in an even more important inflammatory response through the secretion of these factors by skeletal muscle (MCP-1, myostatin. TNF-α, IL-6, IL-10 and IL-1β) [117,118]. It has been suggested that certain myokines induced by inflammation, including irisin, IL-8, IL-15 and FGF21, might play a role in limiting the negative effects of this state on skeletal muscle energy metabolism by enhancing oxidative capacity [23,117]. This mechanism could serve as a balance for the reestablishment of a functional energy metabolism in muscle previously altered by adipose tissue signalling in the context of systemic inflammation. Some myokines are also decreased in chronic low-grade inflammation, such as IL-13 [50], but the mechanisms resulting in the reduction of expression and/or secretion of these myokines remain to be fully understood. Another important source of pro-inflammatory factors in the context of obesity and T2D is intermyocellular adipose tissue (IMAT) and perimuscular adipose tissue (PMAT) [119]. These skeletal muscle fat deposits expand in the context of obesity and it is suspected that they are the source of pro-inflammatory factors involved in chronic low-grade inflammation such as MCP-1 [23,119]. Since this form of adipose tissue is embedded in the muscle tissues, it is difficult to differentiate the effect of the factors secreted by the adipocytes from the metabolic changes induced by factors secreted by the myocytes. IMAT and PMAT could be involved in the development of skeletal muscle IR and/or

mitochondrial dysfunction in the context of T2D through altered adipose tissue signalling [120]. Conditioned media from adipocytes isolated from the IMAT of patients with obesity was shown to reduce insulin signalling and glycogen synthesis in hSkMCs, supporting a role in the development of muscle IR [121]. To our knowledge, this study is the only one to have found a direct causal link between IMAT and the incidence of developing muscle IR. Further observation of the crosstalk between these fat deposits and muscle would be required to further establish the contribution of IMAT and PMAT in muscle metabolic defects found in patients with T2D.

To avoid speculation about the factors inducing changes in myokine secretion in patients with T2D, new studies should be conducted using alternative approaches to the identification of these factors and how they act on skeletal muscle energy metabolism. By measuring the output of molecules from skeletal muscle through the collection of conditioned media from cultured hSkMCs, through microdialysis or muscle targeted blood samples, peptides, metabolites and RNAs collected can be identified as originating directly from muscle and not from other tissues. Then, considering the availability of many new high-throughput methods to collect and analyse data nowadays, conducting a proteomics study on the secretome of skeletal muscle from patients with T2D in comparison to healthy subjects seems essential. This analysis has been achieved by other groups before, but not with a focus on all signalling molecules [122–126]. This approach could allow the visualisation of protein expression networks in clusters, facilitating the formation of new links in the expression or secretion of certain myokines with other myokines. After identifying synergistic effects between two or more myokines, further studies could be conducted with a targeted approach to characterize that relationship and better understand how it influences the development of IR in muscle. Eventually, these steps in validating the pertinence of myokines as a target for the treatment of T2D could lead to the development of new therapies based on either physical exercise targeting the secretion of one or multiple myokines known to be altered in the context of T2D or drugs simulating this effect (i.e. drugs that improve the secretion of one or multiple myokines linked to the development of IR). In fact, a study comparing moderate continuous intensity training (MICT) with high intensity interval training (HIIT) in patients with T2D showed a greater improvement in glucose homeostasis and VO_2max in the HIIT group following the training protocol, even with a reduced training volume and energy expenditure compared to the MICT group [127]. The molecular mechanisms underlying this increased effectiveness of HIIT for the management of T2D in comparison to MICT are not understood. Therefore, it is a possibility that HIIT induces the secretion of certain factors from skeletal muscle that mediate these beneficial effects on muscle metabolism and whole-body insulin sensitivity.

What about the other factors in the skeletal muscle secretome?

At the beginning of 2018, Whitham et al. demonstrated the existence of a skeletal muscle to liver crosstalk during physical exercise mediated through the secretion of extracellular vesicles (EVs) [128]. The EVs were observed to be induced by muscle contraction and transported to the liver, where their content was delivered to hepatocytes. This research group also analyzed the contents of these vesicles to identify the myokines they contained and found many proteins already known to be secreted by hSkMCs. This suggests that skeletal muscle can act as an endocrine organ by secreting factors in a non-traditional manner, meaning not through soluble proteins in circulation, during contraction to influence whole-body energy metabolism. When cultured in vitro, biopsy-derived hSkMCs maintain the metabolic characteristics of their donors (i.e. metabolic flexibility, IR and lipid content) [129,130]. Consequently, muscle cells from patients with T2D maintain their diabetic phenotype in vitro (i.e. IR, impaired mitochondrial functions, incomplete fatty acid oxidation, etc.) [131–137]. To our knowledge, the proteome contained in skeletal muscle EVs of patients with T2D has not been compared to the one from subjects who are insulin sensitive. Since the secretome of hSkMCs from patients with T2D shows altered myokine secretion [23], we hypothesize that the proteins contained in EVs secreted by IR muscle will also be different from insulin sensitive muscle. A study of this particular proteome could allow a better understanding of the molecular mechanisms leading to IR and mitochondrial dysfunction during T2D. It is possible that hSkMCs that display IR and impaired fatty acid oxidation release different factors in their EVs during contraction which mediate an impaired energy metabolism response in the surrounding cells/tissues. In the context of rheumatoid arthritis, another chronic non-communicable disease related to immunometabolism, it has been shown that EVs can be released locally in the musculoskeletal joints to induce acute inflammation [138]. These EVs contain miRNAs that can either induce or inhibit the release of pro-inflammatory cytokines such as IL-6, IL-8 and IL-1β [139]. It is thus possible to hypothesize that similar miRNAs could be released in EVs from skeletal muscle in the context of obesity and/or T2D and could specifically regulate the secretion of certain myokines in surrounding muscle cells, leading to the development of muscle IR and/or mitochondrial dysfunction. It might be important to include in future proteomics studies of skeletal muscle from patients with T2D a component taking into account EVs. This would allow a better understanding of the potential role of these different skeletal muscle signalling factors in the development of T2D-associated muscle metabolic defects.

In addition, it has been shown by many groups that certain metabolites, namely intermediates of fatty acid metabolism, are involved in the development of metabolic defects in skeletal muscle associated with T2D. Certain miRNAs specific to skeletal muscle have also been suggested to be involved in the diabetic phenotype, especially in relation to IR. Many myo-miRNAs (myomirs) have been shown to be either induced or decreased in the context of T2D and these myomirs were identified to be targets of numerous different cell signalling cascades [140]. This points to a role of miRNAs in skeletal muscle signalling leading to the development of T2D. Therefore, these molecules should not be ignored during the analysis of the muscle secretome to better understand how IR and mitochondrial dysfunction occur in patients with T2D. In fact, either myomirs and/or metabolites could be involved in the altered secretion of myokines found in patients with T2D. A study showed that muscle cells could secrete exosomes containing miRNAs that regulated the expression of differentiation factors in myocytes [141]. These miRNAs could then also potentially regulate the expression of certain myokines, as discussed earlier regarding this method of regulation for cytokine production in the context of arthritis. Alterations in the production of these factors could lead to the altered secretion of myokines in skeletal muscle in the context of T2D. Considering this hypothesis, it would be relevant to observe how these myomirs can be induced by muscle contraction to eventually exploit their role on skeletal muscle energy metabolism for the treatment of T2D.

Conclusion

A lot remains to be determined concerning myokine secretion and expression in the context of T2D. Many of the myokines found to be dysregulated in the circulation or muscle of patients with T2D

have yet to be identified as secreted by this tissue. Also, some myokines known to influence muscle energy metabolism still have not been characterized in skeletal muscle affected with IR and/or mitochondrial dysfunction. By establishing the potential candidate myokines induced by exercise that could mediate a maximal attenuation of the muscle metabolic defects found in patients with T2D, exercise programs and/or pharmaceutical treatments could be developed to target the secretion of these molecules. This could serve as a new method of management of T2D focused on skeletal muscle metabolism.

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Disclosure of interest

The authors declare that they have no competing interest.

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